

EMCYT- estramustine phosphate sodium capsule

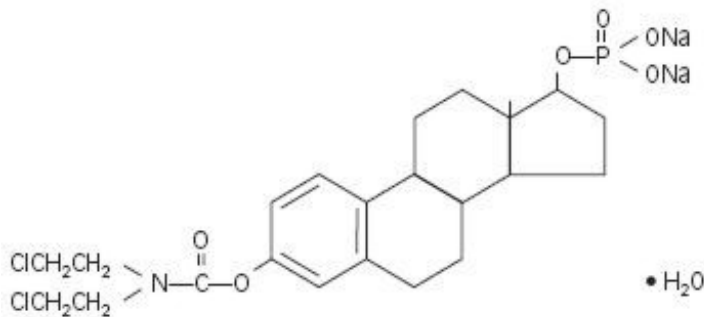
Pharmacia and Upjohn Company

Emcyt[®] estramustine phosphate sodium capsules

DESCRIPTION

Estramustine phosphate sodium, an antineoplastic agent, is an off-white powder readily soluble in water. EMCYT Capsules are white and opaque, each containing estramustine phosphate sodium as the disodium salt monohydrate equivalent to 140 mg estramustine phosphate, for oral administration. Each capsule also contains magnesium stearate, silicon dioxide, sodium lauryl sulfate, and talc. Gelatin capsule shells contain the following pigment: titanium dioxide.

Chemically, estramustine phosphate sodium is estra-1,3,5(10)-triene-3,17-diol(17 β)-,3-[bis(2-chloroethyl)carbamate] 17-(dihydrogen phosphate), disodium salt, monohydrate. It is also referred to as estradiol 3-[bis(2-chloroethyl)carbamate] 17-(dihydrogen phosphate), disodium salt, monohydrate. Estramustine phosphate sodium has an empiric formula of $C_{23}H_{30}Cl_2NNa_2O_6P \cdot H_2O$, a calculated molecular weight of 582.4, and the following structural formula:



CLINICAL PHARMACOLOGY

Estramustine phosphate (Figure 1) is a molecule combining estradiol and nornitrogen mustard by a carbamate link. The molecule is phosphorylated to make it water soluble.

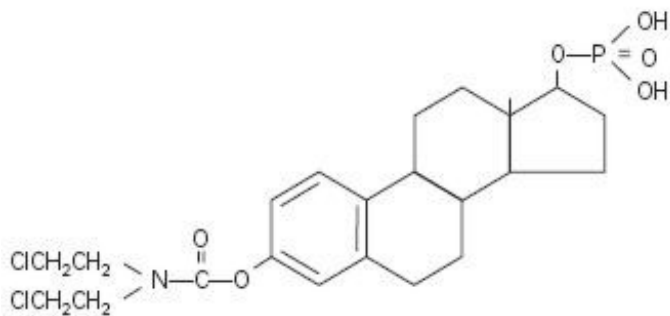


Figure 1. Estramustine Phosphate

Estramustine phosphate taken orally is readily dephosphorylated during absorption, and the major

metabolites in plasma are estramustine (Figure 2), the estrone analog (Figure 3), estradiol, and estrone.

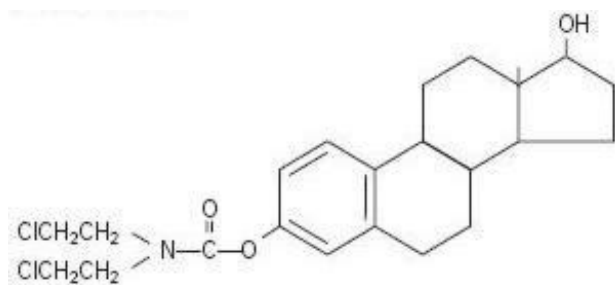


Figure 2. Estramustine

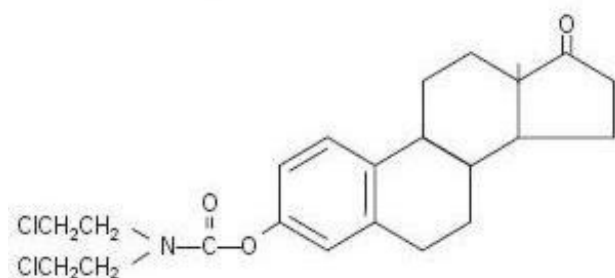


Figure 3. Estrone Analog of Estramustine

Prolonged treatment with estramustine phosphate produces elevated total plasma concentrations of estradiol that fall within ranges similar to the elevated estradiol levels found in prostatic cancer patients given conventional estradiol therapy. Estrogenic effects, as demonstrated by changes in circulating levels of steroids and pituitary hormones, are similar in patients treated with either estramustine phosphate or conventional estradiol.

The metabolic urinary patterns of the estradiol moiety of estramustine phosphate and estradiol itself are very similar, although the metabolites derived from estramustine phosphate are excreted at a slower rate.

INDICATIONS AND USAGE

EMCYT Capsules are indicated in the palliative treatment of patients with metastatic and/or progressive carcinoma of the prostate.

CONTRAINDICATIONS

EMCYT Capsules should not be used in patients with any of the following conditions:

- 1) Known hypersensitivity to either estradiol or to nitrogen mustard.
- 2) Active thrombophlebitis or thromboembolic disorders, except in those cases where the actual tumor mass is the cause of the thromboembolic phenomenon and the physician feels the benefits of therapy may outweigh the risks.

WARNINGS

It has been shown that there is an increased risk of thrombosis, including fatal and nonfatal myocardial

infarction, in men receiving estrogens for prostatic cancer. EMCYT Capsules should be used with caution in patients with a history of thrombophlebitis, thrombosis, or thromboembolic disorders, especially if they were associated with estrogen therapy. Caution should also be used in patients with cerebral vascular or coronary artery disease.

Glucose Tolerance—Because glucose tolerance may be decreased, diabetic patients should be carefully observed while receiving EMCYT.

Elevated Blood Pressure—Because hypertension may occur, blood pressure should be monitored periodically.

PRECAUTIONS

General

Fluid Retention. Exacerbation of preexisting or incipient peripheral edema or congestive heart disease has been seen in some patients receiving therapy with EMCYT Capsules. Other conditions which might be influenced by fluid retention, such as epilepsy, migraine, or renal dysfunction, require careful observation.

EMCYT may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients.

Because EMCYT may influence the metabolism of calcium and phosphorus, it should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency. Patients with prostate cancer and osteoblastic metastases are at risk for hypocalcemia and should have calcium levels closely monitored.

Gynecomastia and impotence are known estrogenic effects.

Allergic reactions and angioedema at times involving the airway have been reported.

Information for the Patient

Because of the possibility of mutagenic effects, patients should be advised to use contraceptive measures.

Laboratory Tests

Certain endocrine and liver function tests may be affected by estrogen-containing drugs. EMCYT may depress testosterone levels. Abnormalities of hepatic enzymes and of bilirubin have occurred in patients receiving EMCYT. Such tests should be done at appropriate intervals during therapy and repeated after the drug has been withdrawn for two months.

Food/Drug Interaction

Milk, milk products, and calcium-rich foods or drugs may impair the absorption of EMCYT.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term continuous administration of estrogens in certain animal species increases the frequency of carcinomas of the breast and liver. Compounds structurally similar to EMCYT are carcinogenic in mice. Carcinogenic studies of EMCYT have not been conducted in man. Although testing by the Ames method failed to demonstrate mutagenicity for estramustine phosphate sodium, it is known that both estradiol and nitrogen mustard are mutagenic. For this reason and because some patients who had been impotent while on estrogen therapy have regained potency while taking EMCYT, the patient should be advised to use contraceptive measures.

ADVERSE REACTIONS

In a randomized, double-blind trial comparing therapy with EMCYT Capsules in 93 patients (11.5 to 15.9 mg/kg/day) or diethylstilbestrol (DES) in 93 patients (3.0 mg/day), the following adverse effects were reported:

	EMCYT n=93	DES n=93
CARDIOVASCULAR-RESPIRATORY		
Cardiac Arrest	0	2
Cerebrovascular Accident	2	0
Myocardial Infarction	3	1
Thrombophlebitis	3	7
Pulmonary Emboli	2	5
Congestive Heart Failure	3	2
Edema	19	17
Dyspnea	11	3
Leg Cramps	8	11
Upper Respiratory Discharge	1	1
Hoarseness	1	0
GASTROINTESTINAL		
Nausea	15	8
Diarrhea	12	11
Minor Gastrointestinal Upset	11	6
Anorexia	4	3
Flatulence	2	0
Vomiting	1	1
Gastrointestinal Bleeding	1	0
Burning Throat	1	0
Thirst	1	0
INTEGUMENTARY		
Rash	1	4
Pruritus	2	2
Dry Skin	2	0
Pigment Changes	0	3
Easy Bruising	3	0
Flushing	1	0
Night Sweats	0	1
Fingertip—Peeling Skin	1	0
Thinning Hair	1	1
BREAST CHANGES		
Tenderness	66	64
Enlargement		
Mild	60	54
Moderate	10	16
Marked	0	5
MISCELLANEOUS		
Lethargy Alone	4	3
Depression	0	2
Emotional Lability	2	0

Insomnia	3	0
Headache	1	1
Anxiety	1	0
Chest Pain	1	1
Hot Flashes	0	1
Pain in Eyes	0	1
Tearing of Eyes	1	1
Tinnitus	0	1
LABORATORY ABNORMALITIES		
Hematologic		
Leukopenia	4	2
Thrombopenia	1	2
Hepatic		
Bilirubin Alone	1	5
Bilirubin and LDH	0	1
Bilirubin and SGOT	2	1
Bilirubin, LDH and SGOT	2	0
LDH and/or SGOT	31	28
Miscellaneous		
Hypercalcemia—Transient	0	1

OVERDOSAGE

Although there has been no experience with overdosage to date, it is reasonable to expect that such episodes may produce pronounced manifestations of the known adverse reactions. In the event of overdosage, the gastric contents should be evacuated by gastric lavage and symptomatic therapy should be initiated. Hematologic and hepatic parameters should be monitored for at least 6 weeks after overdosage of EMCYT Capsules.

DOSAGE AND ADMINISTRATION

The recommended daily dose is 14 mg per kg of body weight (ie, one 140 mg capsule for each 10 kg or 22 lb of body weight), given in 3 or 4 divided doses. Most patients in studies in the United States have been treated at a dosage range of 10 to 16 mg per kg per day.

Patients should be instructed to take EMCYT Capsules at least 1 hour before or 2 hours after meals. EMCYT should be swallowed with water. Milk, milk products, and calcium-rich foods or drugs (such as calcium-containing antacids) must not be taken simultaneously with EMCYT.

Patients should be treated for 30 to 90 days before the physician determines the possible benefits of continued therapy. Therapy should be continued as long as the favorable response lasts. Some patients have been maintained on therapy for more than 3 years at doses ranging from 10 to 16 mg per kg of body weight per day.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.¹⁻⁸ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

White opaque capsules, each containing estramustine phosphate sodium as the disodium salt monohydrate equivalent to 140 mg estramustine phosphate—bottle of 100 (NDC 0013-0132-02).

NOTE

EMCYT Capsules should be stored in the refrigerator at 36° to 46°F (2° to 8°C).

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC, 20402.
2. AMA Council Report, Guidelines for Handling Parenteral Antineoplastics, JAMA. 1985; 253 (11):1590-1592.
3. National Study Commission on Cytotoxic Exposure-Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia. Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia. 1983; 1:426-428.
5. Jones RB, et al. Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA-A Cancer Journal for Clinicians. 1983; (Sept/Oct) 258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm. 1990; 47:1033-1049.
7. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. Am J Hosp Pharm. 1986; 43:1193-1204.
8. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice. Pittsburgh, Pa: Oncology Nursing Society; 1999:32-41.

Rx only



Distributed by

Pharmacia & Upjohn Company

Division of Pfizer Inc, NY, NY 10017

LAB-0088-4.0

June 2007

PRINCIPAL DISPLAY PANEL - 140 mg Capsule Bottle Label

NDC 0013-0132-02

100 Capsules

Rx only

Emcyt®

estramustine phosphate

sodium capsules

140 mg*

Store in refrigerator at 36° to 46°F (2° to 8°C).

Pfizer

Distributed by

Pharmacia & Upjohn Co

Division of Pfizer Inc, NY, NY 10017



NDC 0013-0132-02
100 Capsules Rx only

Emcyt®
estramustine phosphate
sodium capsules

140 mg*

Store in refrigerator at 36° to 46°F (2° to 8°C).

DOSAGE AND USE:
See accompanying
prescribing information.

Each capsule contains
estramustine phosphate
* sodium equivalent to
140 mg estramustine
phosphate.

819 172 202
4201727 02

2006 MADE
IN ITALY



Distributed by
Pharmacia & Upjohn Co
Division of Pfizer Inc, NY, NY 10017



LOT
EXP

PRINCIPAL DISPLAY PANEL - 140 mg Capsule Bottle Carton

NDC 0013-0132-02

100 Capsules

Rx only

Emcyt®

estramustine phosphate
sodium capsules

140 mg*

**Store in refrigerator at 36° to 46°F
(2° to 8°C).**

Pfizer

Distributed by

Pharmacia & Upjohn Co

Division of Pfizer Inc, NY, NY 10017



EMCYT

estrarmustine phosphate sodium capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:00 13-0 132
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name		Basis of Strength	Strength	
ESTRAMUSTINE PHOSPHATE SODIUM (UNII: 75F375MT2N) (ESTRAMUSTINE - UNII:35LT29625A)		ESTRAMUSTINE PHOSPHATE	140 mg	
Inactive Ingredients				
Ingredient Name			Strength	
MAGNESIUM STEARATE (UNII: 70097M6I30)				
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)				
SODIUM LAURYL SULFATE (UNII: 368GB5141J)				
TALC (UNII: 7SEV7J4R1U)				
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)				
Product Characteristics				
Color	WHITE (opaque)	Score	no score	
Shape	CAPSULE	Size	19 mm	
Flavor		Imprint Code	PHARMACIA;AND;UPJOHN;EMCYT;140 MG	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0013-0132-02	1 in 1 CARTON		
1		100 in 1 BOTTLE		
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA		NDA018045	01/01/1992	

Labeler - Pharmacia and Upjohn Company (829076566)

Establishment			
Name	Address	ID/FEI	Business Operations
Pfizer Cork Limited		988786778	API MANUFACTURE(0013-0132)

Establishment			
Name	Address	ID/FEI	Business Operations
Pfizer Italia S.r.l.		431227388	MANUFACTURE(0013-0132) , PACK(0013-0132)

Establishment			
Name	Address	ID/FEI	Business Operations
Valdepharm		260128560	API MANUFACTURE(0013-0132)

Establishment

Name	Address	ID/FEI	Business Operations
Excella GmbH		329809800	API MANUFACTURE(0013-0132)

Revised: 6/2014

Pharmacia and Upjohn Company